

Why Is Environmental Tobacco Smoke More Strongly Associated with Coronary Heart Disease Than Expected? A Review of Potential Biases and Experimental Data

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Despite exposure levels estimated to be equivalent to smoking only 0.1–1.0 cigarettes per day, exposure to environmental tobacco smoke (ETS) is estimated to increase the risk of death from coronary heart disease (CHD) between 25 and 35% above the risk of nonexposed persons. This surprisingly large risk associated with a seemingly small exposure has raised doubts about the validity of attributing the increased CHD risk to ETS exposure. This paper reviews various biases that have been hypothesized to account for the increased CHD risk associated with ETS in the epidemiologic studies and characterizes the adverse effects of ETS on thrombosis, vascular endothelium, and exercise tolerance observed in experimental studies of humans and laboratory animals. None of the identified factors that has been proposed to introduce a spurious association between ETS and heart disease seem to invalidate the epidemiologic findings, either separately or in combination. In addition, experimental studies of ETS and heart disease demonstrate that acute exposure of humans and other species to ETS affects platelet function, vascular endothelium, and myocardial exercise tolerance at exposure concentrations widely prevalent in the workplace. Because exposure to ETS affects multiple physiologic pathways, it appears biologically plausible that ETS could cause the substantial increase in CHD risk that has been observed in epidemiologic studies. **Key words:** atherosclerosis, cardiovascular disease, risk factor, smoking. — *Environ Health Perspect* 107(suppl 6):853–858 (1999).

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Background

Estimates of the number of deaths in the United States from heart disease attributable to exposure to environmental tobacco smoke (ETS) range from 32,000 to 40,000 annually, approximately two-thirds of the estimated 53,000–60,000 deaths from all causes attributed to ETS (1–3). Based on pooled analyses of epidemiologic studies, nonsmokers exposed to ETS in the workplace have an estimated cardiovascular risk 1.35 times that of those not exposed, whereas those exposed at home have a cardiovascular risk 1.23 times that of the unexposed (4). Should these estimates be accurate, ETS exposure would rank as the third leading cause of avoidable death in the United States (1). In addition, these estimates of cardiovascular deaths from ETS are approximately 20% of the estimated 180,000 cardiovascular deaths from active smoking, the leading cause of avoidable death in the United States (5).

The increased risk of cardiovascular disease associated with ETS exposure has been viewed as disproportionately large compared to the risk caused by active cigarette smoking, especially when ETS exposure is considered in terms of cigarette equivalents (6–8). The National Research Council estimates that nonsmokers exposed to ETS absorb the equivalent of 0.1–1.0 cigarettes actively smoked per day, based on urine cotinine measurements (9). Thus, nonsmokers exposed to ETS absorb an estimated 1% of the nicotine of people actively smoking one pack per day, yet they experience up to 50%

the excess risk of heart disease incurred by active smokers (7).

This paper considers the apparent discrepancy between the risk estimates for active and passive smoking. First, it examines several possible methodological problems or biases that have been hypothesized to explain the strength of the observed association between ETS and heart disease, including publication bias, residual confounding, and exposure misclassification. Second, it considers explanations as to why the ETS/CHD (coronary heart disease) relationship might be larger than expected based on cigarette equivalents. Within this section we discuss *a*) the magnitude of the association that might be expected based on studies of active smoking; *b*) the dose–response relationships measured between ETS exposure and platelet function, vascular endothelium, and cardiac exercise tolerance in experimental studies; *c*) discrepancies between ETS and mainstream smoke regarding certain components of ETS exposure that are not captured accurately by the measure of cigarette equivalents; and *d*) why the effects of ETS on active smokers may differ from the effects on nonsmokers.

Bias, Confounding, and Misclassification of Exposure

This first section examines various methodological considerations that could, in theory, cause the epidemiologic studies to over- or underestimate the association between ETS exposure and heart disease. One of these issues (publication bias) relates to the general

scientific process, external to any particular study, whereas other issues such as confounding and misclassification of exposure affect the magnitude of the association in specific studies.

Publication Bias

It is possible that studies finding a significant effect (or even nonsignificant effects in the anticipated direction) are more likely to be developed into manuscripts by investigators and subsequently more likely to be accepted for publication. This publication pattern is referred to as publication bias. It has been suggested that the omission from the literature of negative studies regarding ETS and heart disease could bias meta-analyses upward and cause a spurious association between ETS and CHD (10–13).

The report by LeVois and Layard (10) discusses publication bias most thoroughly. The authors argue that the exclusion of large unpublished studies, specifically the American Cancer Society's Cancer Prevention Study I (CPS-I) and II (CPS-II) and the National Mortality Followback Study, from the reports estimating the impact of ETS on heart disease (1–3) introduces publication bias. Using a graphical approach to detect publication bias (14), LeVois and Layard demonstrate that the inclusion of these unpublished studies (at the time of LeVois and Layard's writing) provides evidence of such bias. However, LeVois and Layard rely on their own analyses of the three studies to support their case. In their analysis of CPS-II, they emphasize the lack of evidence that heart disease death rates are increased among lifelong nonsmokers married to smokers [relative risk (RR) = 0.97 for men and 1.00 for women] (10).

More important is that CPS-II never smokers married to current smokers do have increased death rates from CHD (RR = 1.22 for men, 95% confidence intervals [CI] 1.07–1.40; and RR = 1.10 for women, 95% CI = 0.97–1.45), as shown by Steenland et al.

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(15). Current exposure to ETS provides a better index of exposure since some of the adverse cardiovascular effects of tobacco smoke are reversible.

With the 1996 Steenland et al. publication (15) describing the impact on cardiovascular risk of ETS exposure in the CPS-II cohort, the interpretable data from the largest prospective cohort studies have now been reported, making the argument of publication bias less plausible. More important, the role of publication bias on the estimated risk associated with ETS has been reviewed, and found to be, at most, small (16). Because of the large number of published studies, the inclusion or exclusion of other unpublished studies would have minimal effect on the overall association between ETS exposure and heart disease risk.

Confounding

It has been argued that individuals who report exposure to ETS also have on average greater exposure to other risk factors that place them at excess risk for CHD (12,17,18). Lee (12) argues that there are well over 100 factors that have been reported to show a significant relationship with cardiovascular disease, and that not all of these factors have been measured and adjusted for in the studies reported. Some of the epidemiologic studies of ETS adjust only for age and sex; most do not capture or control completely for other factors that may contribute to risk. The resulting overestimation of risk attributable to ETS is called residual confounding.

Although residual confounding is of concern, there is little to suggest that it contributes more than a small fraction of the observed association between ETS and CHD. Few of the more than 100 factors associated with increased CHD risk contribute independently to the risk (19). The lifestyle factors that independently affect CHD risk and are associated with ETS exposure do not all affect the ETS association in the same direction. For example, alcohol consumption is more common among persons who report ETS exposure but is generally associated with decreased rather than increased CHD risk. Adjusting for all measured covariates in the epidemiologic studies of ETS generally causes either a small increase or decrease in the observed association. In the Nurses' Health Study, which has the best potential to adjust for dietary factors, the age-adjusted relative risk for CHD associated with ETS exposure was 1.97 (20). Further adjustment for a broad array of risk factors (alcohol intake, body mass index, history of hypertension, diabetes mellitus, hypercholesterolemia, menopausal status, current use of postmenopausal hormones, past use of oral contraceptives, vigorous exercise, fat intake, vitamin E intake, aspirin use, parental

history of myocardial infarction [MI], and father's occupation when the participant was 16 years of age) reduced the excess relative risk by only 26% to 1.71 (20). This list includes most of the major risk factors for heart disease (19). Residual confounding is unlikely to account for the remaining 74% of the unadjusted association.

Misclassification of Smoking Status

There is a well-known tendency for the prevalence of cigarette smoking to be underestimated when assessed by self-report (21–23). In general, nonrandom misclassification of the independent variables in analysis will tend to bias estimates toward the null, leading to the underestimation of the ETS/CHD relationship. This bias toward the null will be the case if the misclassification of the risk factor is random, that is, if people are as likely to over report as to under report their exposure to ETS. However, if the misclassification is differential (i.e., not random), then it is possible that misclassification can bias an estimate away from the null hypothesis.

It has been suggested that assessment of the effects of ETS exposure, independent of active smoking, is a case in which differential misclassification could be of concern (21). It is possible that a larger proportion of active smokers who incorrectly report that they are nonsmokers may also report that they are exposed to ETS. In this case, an analysis of the impact of ETS among reported nonsmokers would include a larger proportion of active smokers among those reporting exposure to ETS than among those not reporting such an exposure. Since the potential impact of active smoking is substantially larger than the impact of ETS, this relative enrichment of those reporting exposure to ETS will increase the risk of disease in that group.

This misclassification is likely to play a relatively minor role in the estimation of the ETS/CHD association. First, its extent has been shown to be relatively small. CARDIA (Coronary Artery Risk Development in Young Adults) is a longitudinal study of the evolution of cardiovascular risk factors in a cohort of young adults. The study includes 5,115 adults age 18–30 at baseline (conducted in 1985–1986) sampled from four communities in the United States. Approximately one-fourth of the sample is African American male, African American female, white male, and white female. This study is one of the few large population-based cohorts to confirm self-reported active smoking with a serum cotinine assay. In this report, the biracial (black and white) CARDIA population is limited to 3,445 nonsmoking men and women age 18 to 30 years. Although the participants are somewhat younger than the participants in the larger

epidemiologic studies used to establish the ETS/CHD association, the CARDIA study offers one of the few opportunities to assess the misclassification of reported active smoking and ETS exposure. Self-reported active smoking rates underestimated the true smoking rate, as assessed by serum cotinine, by only 1.3% overall (although the misclassification rate was somewhat higher in subgroups, such as 3.3% in African Americans with less than a high school education) (23). Thus, few active smokers reported themselves to be nonsmokers, lessening concern that a large number of those classified as nonsmokers exposed to ETS are in fact active smokers. More important, the magnitude of relative risk of heart disease associated with active smoking (averaging approximately 1.8 across all ages) is relatively low, and the potential consequences of this type of error are small, particularly in comparison to the potential consequences in studies of ETS and lung cancer. This smaller effect has led Lee, who initially raised this concern in the assessment of the ETS/lung cancer relationship (21), to conclude that this bias could not explain the overall estimate of the relative risk of 1.28. At most, misclassification bias has only a very minor role in affecting the ETS/CHD association.

Other Biases

Those participants in case-control studies with a disease (cases) may be more likely to remember the exposure of interest (ETS) than those without the disease (controls), which introduces a recall bias (12). It is also possible that surrogates in case-control studies may misreport exposures differentially, leading to an overestimation of the ETS/CHD relationship (13). With growing evidence from prospective cohort studies (in which exposure is established directly by the participant prior to the development of disease) to describe the ETS/CHD relationship, recall bias and surrogate reporting effects are unlikely to have a significant effects on risk estimates. In general, misclassification of the disease status will bias results toward the null (in this case underestimating the ETS/CHD relationship). Springall has speculated that persons with ETS exposure may differentially be diagnosed as having heart disease because of lifestyle or occupational factors associated with heart disease (13). However, this seems implausible given the routine nature of diagnostic tests for heart disease and the lack of evidence to support differential misclassification.

Summary of Potential Biasing Effects

Although several potential biases could cause an over- or underestimation of the ETS/CHD effect, these seem unlikely, individually or in combination, to account for the observed

association. The potential impact of any of these individual factors is small, largely speculative, and, as illustrated by alcohol consumption, not uniformly in one direction. Even though it is theoretically possible that the combined effect of these factors could explain the ETS/CHD relationship, the lack of evidence for any individual factor makes it unlikely that an aggregate effect can be invoked to explain the ETS/CHD association. At most, the composite impact of these biases would only marginally decrease the estimated effect of ETS.

Potential Explanations for the ETS/CHD Relationship

The next section of this paper examines why the ETS/CHD relationship might be larger than expected based on cigarette equivalents. It considers extrapolations from studies of active smoking, experimental studies that measure the acute effects of ETS on platelet function, vascular endothelium, and exercise tolerance, and differences in the composition of ETS and mainstream smoke that complicate extrapolation from active smoking to ETS based on cigarette equivalents.

Extrapolation from Studies of Active Smoking

Many studies describe a dose-response relationship between the risk of CHD and the number of cigarettes smoked per day by active smokers (24). Data from the 1983 Surgeon General's report on smoking and cardiovascular disease can be used to predict the expected hazard ratio at a low-dose exposure of 0.1–1.0 cigarettes per day [Table 12 in Section 3 of the U.S. DHHS report (24)]. This report summarizes nine studies in males, providing the mortality ratio for coronary disease in relation to the number of cigarettes consumed. We used linear regression to describe the relationship between cigarette use and CHD mortality in the seven studies that report risk in relation to cigarettes per day (allowing more direct comparison to the dose in ETS smoking) and three or more levels of smoking (allowing meaningful regression analysis). For this analysis we assumed a linear relationship between cigarette use and the mortality ratio for CHD. For each study, the cigarette exposure was described as the mid-point of the range of exposure (for example, for those smoking 1 to 9 cigarettes per day, a value of $[1 + 9]/2$ or 5 cigarettes per day was used). For the upper open interval, a value one-half the range of the second highest interval above the lower limit was used. For example, if the second highest interval was 21 to 39 cigarettes per day, with a range of 18, then the value of 49 (9 above the lower limit of the top interval) was used in the analysis. Linear regression was then used to estimate

the expected value of the mortality ratio at 0.55 cigarettes per day (the midpoint of the interval 0.1 to 1.0 cigarettes per day). The expected mortality ratio ranges from 1.13 to 1.47 across the seven studies, with an overall average of 1.32, not substantially different from the projection expected based on cigarette equivalent exposures to ETS. A similar approach by Law et al. (7) also found a slight difference between the expected RR estimates, based on projections from active smokers, and the observed RR estimates, based on studies of ETS exposure.

Extrapolations based on the CHD risk of active smokers are subject to a number of uncertainties, however. Although the RR for CHD is strongly and inversely related to age (25), these calculations are based on age-adjusted, rather than age-specific RR estimates for the active smokers. Similarly, our projection and that of Law et al. (7) are based on studies of active smoking in the 1950s and 1960s, when the association between cigarette smoking and CHD in the United States was weaker than it became by the 1980s (25). Finally, there is uncertainty about the appropriate intercept for these mathematical models. Nevertheless, these extrapolated risks are closer to the directly measured risks of ETS exposure reported in the epidemiologic literature (4).

Experimental Studies of ETS Exposure

Experiments in both humans and animals demonstrate that ETS exposure adversely affects several pathways involved in the pathogenesis of CHD (26). The experimental studies are an important complement to the epidemiologic studies because they minimize the potential for confounding by measuring changes within individuals before and after acute ETS exposure and because the level and duration of ETS exposure are reasonably well characterized. The experiments are particularly informative regarding mechanism, dose response, and biologic plausibility. These studies have measured effects on platelets, thrombosis, vascular endothelium, and exercise tolerance. In particular the effects of ETS on platelets might amplify the adverse cardiovascular effects of ETS above those expected based on cigarette equivalents.

Platelets and thrombosis. The acute event that precipitates many MIs (heart attacks) is the formation of a thrombus or clot that obstructs the arterial blood supply to a portion of the heart (27). ETS exposure enhances the activation and aggregation of platelets, which have an initiating role in thrombus formation. The inhibition of platelet aggregation by aspirin and other antiplatelet drugs is thought to underlie the prevention of cardiovascular events in high-risk populations (28,29).

At least five experimental studies have measured the acute effects of ETS exposure on platelet function among healthy, non-smoking human volunteers exposed for 15 to 60 min at ETS concentrations comparable to those in many bars, restaurants, and other public places (Table 1). These studies measured changes in platelet aggregation, platelet sensitivity to antiaggregatory prostaglandins (PGI₂) or concentrations of proaggregatory prostaglandins such as thromboxane B₂. For example, Krutz and Sinzinger (30) observed an increase in markers of platelet activation and a decrease in platelet sensitivity to PGI₂ among 12 nonsmokers exposed for 20-min in an 18 m³ room in which 30 Gitanes had recently been smoked. The hypercoagulable state demonstrated among nonsmokers acutely exposed to ETS (30–34) resembles the acute changes in smokers who consume one or two cigarettes after a period of abstinence (35–43). Schmid et al. (31) found that, prior to ETS exposure, the platelets of nonsmokers were significantly less activated than those of smokers, whereas after 20 min exposure to ETS, platelet activation increased among the nonsmokers exposed to ETS ($p < 0.01$) but remained constant among the active smokers ($p > 0.05$). The effects of tobacco smoke exposure upon platelet aggregation and production of thromboxane B₂ appear to be mediated by factors other than nicotine (44).

Experimental exposure of rabbits (45) and rats (46) to low concentrations of ETS has also been shown to shorten bleeding time, another measure of platelet activation (26). The average concentrations of air nicotine, carbon monoxide, and total particulate concentrations in rabbits exposed to low-dose ETS were 30 µg/m³, 18.8 ppm, and 4.0 ppm, respectively. Bleeding time was shortened as much in rabbits exposed to low as to higher concentrations of ETS (45). Another experiment involving New Zealand white rabbits demonstrated that 15 min of exposure to sidestream cigarette smoke significantly increased tracheal epithelial production of several prostaglandins that affect platelet aggregation including prostaglandin (PG)E₂, 6-keto F_{1α}, and thromboxane B₂ (47).

Effects on vascular endothelium. Injury to the endothelial layer of blood vessels is another mechanism by which relatively small exposures to ETS could contribute to the initiation or promotion of atherogenesis (48). ETS profoundly damages the vascular endothelium in animal models, inducing bleeding, microvillus-like projections from the luminal surface, and the presence of micro-thrombi in low shear areas of rats (49). Experimental data on vascular endothelial injury are more limited in humans, although Davis et al. (32) (Table 1) found an increase

Table 1. Experimental studies of ETS effects on platelets, endothelial cells, and cardiac performance in humans.

Reference	Place	Population	Exposure	Duration	Results
Effects on platelets					
Kritz and Sinzinger, 1996 (30)	Vienna, Austria	12 nonsmokers	30 Gitanes in 18-m ³ room	20 min	↑ platelet activation ↓ platelet sensitivity to PGI ₂
Schmid et al., 1995 (31)	Vienna, Austria	12 nonsmokers, age 20–32	30 Gitanes in 18-m ³ room	60 min	10–50% acute ↑ in plasma thromboxane B ₂ Mostly reversed in 6 hr Measurements in nonsmokers after repeated exposures resembled those of smokers
Davis et al., 1989 (32)	Kansas City, KS	10 nonsmoking men, age 23–49	Hospital corridor next to smokers	20 min	↓ in platelet aggregate ratio from 0.87 to 0.78 (reflects ↑ formation of platelet aggregates)
Burghuber et al., 1986 (33)	Vienna, Austria	9 nonsmoking men, age 25–40	30 Gitanes in 18-m ³ room	20 min	↓ platelet sensitivity to PGI ₂
Sinzinger and Kefalides, 1982 (34)	Vienna, Austria	9 nonsmokers, age 24–30	30 Gitanes in 18-m ³ room	15 min	↓ platelet sensitivity to antiaggregatory prostaglandins
Effects on endothelial cells					
Davis et al., 1989 (32)	Kansas City, KS	10 nonsmoking men, age 23–49	Hospital corridors next to smokers	20 min	↑ in circulating anuclear endothelial cell carcasses from mean ± SD 0.28 ± 0.9 to 3.7 ± 1.1
Effects on cardiac performance					
Leone et al., 1991 (60)	Italy	19 nonsmoking men (9 healthy, 10 MI)	15–20 cigarettes smoked in a 60-m ³ room	2-hr exposure followed by exercise stress test	No effect on 9 healthy men In men with hx MI peak exercise power ↓ 33% Time to recovery ↑ 41%
McMurray et al., 1989 (61)	North Carolina	8 healthy women (4 smokers, 4 nonsmokers)	Machine smoking 2 cigarettes per 6 min	Exercise stress test in room where 15–20 cigarettes smoked	Time to exhaustion ↓ 8% Max oxygen uptake ↓ 10%
Aronow, 1978 (62)	Long Beach, CA	10 men (8 ex-smokers, 2 smokers) with stable exertional angina	2 hr in 30.8-m ³ room with 3 companions who smoked 5 cigarettes	Bicycle ergometry test	Time to angina ↓ 38% in unventilated room and ↓ 22% in well ventilated room

SD, standard deviation.

in circulating anucleated endothelial cells in response to ETS exposure. These circulating cells, which may reflect acute endothelial desquamation, become almost as abundant in persons exposed to ETS as in active smokers. Exposure of nonsmokers to ETS might also contribute to vascular injury by causing an acute decrease in serum ascorbic acid and protein sulfhydryl group concentrations, accelerated lipid peroxidation, and accumulation of low density lipoprotein cholesterol in macrophages (50).

Passive smoke exposure has been shown to accelerate arteriosclerotic plaque development in experimental studies of cockerels (51–54), rabbits (55,56), and rats (57). There is some evidence from cockerels that the size of the plaques is influenced more than the number of plaques (52) and that components of the vapor phase of ETS may accelerate atherogenesis more than does the tar fraction (53,54). Exposure to the sidestream smoke from even one cigarette was sufficient to promote atherosclerotic plaque development in cockerels (51). These adverse effects on vascular endothelium and plaque development observed in the experimental studies could contribute to the dose-dependent impairment of vascular dilatation triggered by the endothelium, that has been seen in some (58), but not all (59),

observational studies of otherwise healthy young adults exposed to ETS.

Effects on cardiac exercise tolerance.

Table 1 lists three experimental studies involving humans. These studies measured changes in exercise tolerance or time to angina in patients with or without a history of cardiovascular disease following exposure to ETS (60–62). The reduction in exercise tolerance was greater among men with a history of a past MI (60) and in those with stable exertional angina (61) than among healthy women in Italy (62). In all these studies, cardiac response to exercise was significantly worsened by ETS exposure.

Inappropriate Representation of Exposure by Cigarette Equivalents

Measurements of urine cotinine in active and passive smokers show that reliance on cigarette equivalents as the sole index of tobacco smoke exposure may substantially underestimate exposure to other constituents of ETS and misrepresent its cardiovascular pathogenicity (9). The composition of ETS is complex, containing over 4,000 chemical compounds with varying representation in sidestream smoke (63). For example, between 2.1 and 46 mg of nicotine (the premetabolite of cotinine) is contained in the undiluted mainstream smoke of each

cigarette. However, the concentration of nicotine is between 1.3 and 21 times greater in undiluted sidestream than in mainstream smoke. Other chemicals have even higher proportionate representation in sidestream smoke. For example, the estimates of the ratio of *N*-nitrosodimethylamine in sidestream to mainstream smoke range from 20 to 130 times, and benzo[*a*]pyrene ranges from 2.5 to 20 times (63). Based on the lower limits of benzo[*a*]pyrene, it is nearly twice as concentrated as nicotine in sidestream smoke. The lack of symmetry between nicotine and other components of mainstream and sidestream smoke is compounded in the cotinine studies by differences in the absorption and metabolism of nicotine. Thus, estimates of exposure based on a single component of ETS may misrepresent the extent of exposure to other components.

Some compounds that are over-represented in sidestream smoke may contribute biologically to the development of clinical coronary events. For example, Glantz and Parmley (26) reported that several animal studies have established a role of aromatic hydrocarbons (including benzo[*a*]pyrene) with the development of atherosclerosis through mechanisms of cell injury and hyperplasia.

Effects of ETS in Smokers and Nonsmokers

Some studies suggest that active smokers may be less adversely affected by ETS than nonsmokers. Glantz and Parmley (26) have observed that the concentrations of certain antioxidants are much higher in the lungs of hamsters exposed to ETS and in active smokers than in lungs of those not exposed chronically to cigarette smoke. These researchers hypothesize that chronic exposure to cigarette smoke may stimulate protective scavenging systems, and therefore smokers may be less sensitive to damage from free radicals in ETS than nonsmokers. They also describe greater activation of lung neutrophils in nonsmokers than in smokers after ETS exposure. Inappropriately activated neutrophils release oxidants involved in tissue damage. Although data are not available to strongly support this potential hypothesis, it may be speculated that the absence of compensatory mechanisms may cause nonsmokers to be more susceptible to ETS than active smokers.

Conclusions

We find little or no evidence that the association between ETS and heart disease observed in numerous epidemiologic studies can be attributed to chance or to various biases that have been proposed. A sufficient number of large epidemiologic studies have now been identified that chance and publication biases have become implausible. Even if additional studies were reported or conducted in the future, these would be unlikely to cause a substantial change in the pooled RR estimate. Confounding also seems unlikely to explain more than a small fraction of the observed association. All of the epidemiologic studies of CHD and ETS exposure control for age and sex. Studies that have adjusted for additional factors have not found large or consistent changes in their relative risk estimates. Even the Nurses' Health Study, which has the most extensive data available to control for diet and other factors, found only a 26% reduction in the excess relative risk after adjusting for 11 covariates (20). The experimental studies of ETS and heart disease that are much less susceptible to confounding or misclassification of exposure than the epidemiologic studies also demonstrate changes in platelet function, vascular endothelium, and myocardial exercise tolerance in response to well-defined exposures to ETS.

There is legitimate uncertainty about the extent to which the association between ETS and heart disease in the epidemiologic studies exceeds what would be expected, based on a linear extrapolation from active smokers. Although the concentration of serum cotinine in nonsmokers exposed to ETS is between 0.1 and 1% of the cotinine concentration in active

smokers, there is no evidence that nicotine alone is the main contributor to heart injury or that nicotine absorption accurately reflects the uptake of other toxicants from ETS.

The experimental studies of ETS and heart disease in humans, although small, provide an unusual resource rarely available for industrial pollutants. These experiments demonstrate that it is biologically plausible that ETS affects platelet function, vascular endothelium, and myocardial exercise tolerance at exposure concentrations widely prevalent in the workplace. These experimental studies share two shortcomings: *a*) they are based on relatively few study subjects; and *b*) because of time limitations, they tend to focus on the effects of acute (rather than chronic) exposure to a relatively few cigarettes. However, although these studies are based on few subjects, they generally have a sufficient number to establish the significant effect of ETS exposure. In addition, the acute effects observed may increase the risk of coronary events both through acute (such as platelet aggregation) and chronic (such as plaque formation) mechanisms. There is also a possibility that a threshold effect may exist, such as leave open the possibility of a threshold effect such as could be observed by increased coagulability after passive smoke exposure. Because ETS affects multiple physiologic pathways, it is entirely plausible that the dose-response relationship is not linear over the entire range of exposure.

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